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Transdermal Nitroglycerin Reduces the Frequency of Anginal Attacks but Fails to Prevent Silent Ischemia

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Objectives. **The aim of this study was to objectively evaluate the effects of intermittent administration of transdermal nitroglycerin on effort tolerance, frequency of anginal attacks and presence of silent ischemic events that occur during normal daily activities.**

Background. **Previous studies have shown that transdermal nitroglycerin patches reduce the incidence of anginal attacks and improve exercise capacity when given intermittently. However, no carefully controlled studies are available on the effects of these preparations (and their dosing schedule) on the occurrence of "silent" ischemic events during unrestricted daily activities.**

Methods. **Twelve men with chronic stable angina, a positive exercise test result and significant coronary artery disease completed a randomized, double-blind, placebo-controlled trial in which patches were worn either continuously or with overnight (8 h) removal. The effects of treatment were objectively assessed by both treadmill exercise testing and 24-h ambulatory electrocardiographic monitoring.**

Results. **Only the intermittent dosing schedule afforded a small but significant improvement in exercise tolerance and prolonged exercise duration and time to ST segment depression. The frequency of anginal attacks was also reduced by both the continuous and intermittent treatment, but the effects on symptoms were not paralleled by a concomitant reduction in ischemic episodes recorded during ambulatory monitoring.**

Conclusions. **The results indicate that when used as monotherapy, intermittent transdermal nitroglycerin preparations lessen symptoms but are ineffective for the long-term prophylaxis of silent myocardial ischemia.**

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The controversies concerning the role of transdermal nitroglycerin preparations for the treatment of angina pectoris (1–6) arise from the evidence that even though these agents afford some benefit during the first phase of treatment (7–10), they very rapidly induce tolerance in many patients (4,11–13). Because the loss of efficacy occurs despite relatively constant plasma levels, the development of tolerance has been related to the pharmacokinetic profile of these drugs, which results in active plasma levels for prolonged periods of time (14).

The results of previous studies (15–20) employing intermittent dosing schedules and assessing drug efficacy by exercise testing and subjective symptoms seem to support this hypothesis. However, little information is available as to whether intermittent transdermal nitrates provide sufficient protection against the silent ischemic events that occur during daily activity (6,21,22) and invariably outnumber anginal attacks (23–27). Furthermore, it is still debated whether discontinuous treatment results in exacerbation of ischemia in the drug-free periods.

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Methods

Study patients. The original study group comprised 14 men (mean age 63 ± 6 years, range 54 to 72) with chronic stable angina and significant coronary disease (≥50% diameter reduction) documented by both coronary arteriography and thallium-201 stress/rest myocardial perfusion scintigraphy. In all 14 patients, a treadmill exercise test (modified Bruce protocol) resulted in angina or significant ischemic ST segment depression (≥1 mm rectilinear or downsloping), or both. Evidence of daily episodes of ischemia (≥1/24 h) during unrestricted activities was also obtained in all patients by Holter monitoring. Patients with recent (≤3 months) myocardial infarction, unstable or variant angina or electrocardiographic (ECG) abnormalities at rest preventing the interpretation of ST segment changes were excluded.

All antianginal medications were withdrawn ≥5 days before the beginning of the study and only sublingual nitroglycerin was allowed for the relief of angina. The clinical characteristics of the study patients are listed in Table 1.

Study design. We conducted a randomized, double-blind, placebo-controlled crossover trial organized in two phases (immediate and maintenance) preceded by a 5-day washout period and lasting 3 and 24 days, respectively.

The efficacy of transdermal nitroglycerin on exercise end points was verified on days 1 and 3 of the immediate phase in which an active (10-mg nitroglycerin) or matching placebo

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Table 1. Clinical Characteristics of the Original Study Group of 14 Men

Pt No.	Age (yr)	Angina: Duration (mo)	Angina: Attacks/Week (no.)	Previous MI	Htn	Diabetes	Vessels With CAD by Angiography (no.)
1	67	60	15	—	–	–	1
2	63	3	5	Inf	–	–	2
3	65	60	6	Inf	+	+	3
4	70	5	10	—	–	+	2
5	62	12	1	nQ	–	–	2
6	67	156	15	—	+	–	1
7	55	8	4	Inf	–	+	3
8	69	12	7	Inf	–	–	3
9	57	6	3	Ant	+	+	2
10	67	60	12	nQ	–	–	2
11	57	3	1	Ant	–	+	2
12	72	16	3	—	+	–	2
13*	54	1	5	—	–	–	2
14*	62	60	17	Inf	+	+	3

*Patient (Pt) withdrew from the study because of severe headache. Ant = anterior; CAD = coronary artery disease; Htn = hypertension; Inf = inferior; MI = myocardial infarction; nQ = non-Q wave infarction; – = no; + = yes.

patch was applied in a randomized, double-blind fashion at 8 AM. To avoid potential carryover effects from active treatment, patients always received a placebo patch on day 2.

The maintenance phase consisted of two periods of 12 days each during which transdermal nitroglycerin (10 mg) was given either continuously or intermittently. In each period, the patients applied two patches a day, the first from 8 AM to midnight to cover the entire active period of the patients and the second from midnight to 8 AM. During the continuous phase, both morning and evening patches were active, whereas during the intermittent phase, the morning patch was active and the evening patch was placebo. Therefore, assuming a constant and complete release of the drug administered during the two periods, the nitroglycerin dose was 10 and 6.6 mg, respectively, over 24 h. Patients were randomized to the two treatment periods in a double-blind crossover design.

Exercise testing. Exercise stress tests were performed at the end of the washout period, on days 1 and 3 of the immediate phase and on day 12 of each period of the maintenance phase. Each test was carried out on the treadmill in the fasting state at noon 4 h after the morning patch application, according to the modified Bruce protocol. All tests were performed by using a computer-assisted unit (Case 12, Marquette Electronics Inc). The 12-lead ECG and blood pressure were recorded every minute throughout exercise and recovery. Leads III, V_1 and V_5 were continuously monitored and the level of the ST segment was automatically calculated in all 12 leads, at the J point and 80 ms thereafter, following signal averaging over 32 beats. Exercise was discontinued whenever ≥1.5 mm of horizontal or downsloping ST segment depression, angina, fatigue, severe arrhythmia or ≥10 mm Hg decrease in blood pressure occurred.

For each test, systolic blood pressure, heart rate and rate-pressure product were recorded at rest, at 1 mm of ST segment depression and at peak exercise. Time to 1 mm of ST segment depression and to peak exercise was also evaluated.

Holter monitoring. Twenty-four hour Holter recordings were performed on days 1 and 3 of the immediate phase, as well as on days 12 and 24 of the maintenance treatment period and were started at 8 AM. The two ECG leads exhibiting maximal ST segment depression during the exercise test were used for the ambulatory study. Leads with abnormal Q waves were avoided and recordings were made in the supine, prone, standing and sitting positions to establish the effects of postural changes on the ST segment.

Patients were instructed to keep a daily diary, describing their activities and recording the time and duration of anginal episodes and nitroglycerin consumption. Painful episodes were identified from the event marker operated by the patients and from diary cards. The two ECG leads were continuously recorded on dual-channel amplitude-modulated recorders (Series 8500, Marquette Electronics Inc.). Episodes of ST segment depression were identified both by reviewing tapes on a memory oscilloscope at a playback speed of 60 times the real time and by analyzing dual-channel high resolution ST trends produced by the internal algorithm of the processing unit (Series 8000/T, Marquette Electronics Inc.). For each episode identified, ECG strips were printed at a paper speed of 25 mm/s together with the preceding and following minute of recording. Only episodes of transient rectilinear or downsloping ST segment depression of ≥1 mm were considered significant.

Data analysis. The end points achieved in each treatment phase were compared with those obtained with placebo. For all tested variables, data were expressed as mean ± SD.

Table 2. Hemodynamic and Ergometric Variables

	Immediate Phase			Maintenance Phase	
	No Patch	Placebo	Active	Continuous	Intermittent
Rest					
HR (beats/min)	70 ± 7	71 ± 8	82 ± 9*	74 ± 6	85 ± 8*
SBP (mm Hg)	145 ± 15	136 ± 12	121 ± 9*	130 ± 20	120 ± 12†
RPP	101 ± 17	97 ± 15	99 ± 11	96 ± 15	102 ± 18
1 mm ST ↓					
HR (beats/min)	112 ± 15	117 ± 13	122 ± 18	119 ± 13	125 ± 14†
SBP (mm Hg)	165 ± 18	160 ± 20	164 ± 13	167 ± 21	170 ± 11†
RPP	185 ± 22	187 ± 31	200 ± 40	199 ± 25	212 ± 28
Time (s)	395 ± 240	471 ± 226	590 ± 213†	540 ± 251	601 ± 236*
Peak ex					
HR (beats/min)	126 ± 14	121 ± 20	125 ± 17	123 ± 24	128 ± 19
SBP (mm Hg)	168 ± 16	160 ± 22	165 ± 18	167 ± 16	170 ± 11
RPP	202 ± 30	194 ± 41	206 ± 43	205 ± 37	218 ± 30
Time (s)	470 ± 212	562 ± 227	631 ± 219	610 ± 231	651 ± 213*

*$p < 0.01$. †$p < 0.05$. HR = heart rate (beats/min); RPP = rate-pressure product (beats/min × mm Hg × 100); SBP = systolic blood pressure (mm Hg); Time = time (s); 1 mm ST ↓ = 1 mm of ST segment depression.

Statistical significance was evaluated by paired two-tailed Student *t* tests. A p value < 0.05 was considered statistically significant.

Results

Of the 14 patients, 12 completed the trial and 2 discontinued active treatment because of severe headache.

Hemodynamic effects at rest (Table 2). In the immediate treatment phase, systolic blood pressure was significantly ($p < 0.01$) lower after active patch application (121 ± 9 mm Hg) than after both placebo administration (136 ± 12 mm Hg) and the no patch period (145 ± 15 mm Hg). In the same period, heart rate levels were higher (82 ± 9 beats/min) than during no patch and placebo (70 ± 7 and 71 ± 8 beats/min, respectively, $p < 0.01$).

In the maintenance treatment phase, a decrease in systolic blood pressure was only noted during intermittent therapy, when this variable was lower (120 ± 12) than on no treatment (145 ± 15 mm Hg, $p < 0.05$). Relative to no treatment (70 ± 7 beats/min), heart rate also increased significantly during intermittent therapy (85 ± 8 beats/min, $p < 0.01$); furthermore, heart rate was higher during intermittent than during continuous dosing (74 ± 6 beats/min), although the difference was not statistically significant. Finally, the values of rate-pressure product were not significantly different in the different phases of maintenance treatment.

Exercise tolerance. In all patients, the exercise test result was positive in the no patch period and remained positive throughout the trial. Angina occurred in three patients during placebo, three during acute patch application, four during continuous and one during intermittent treatment. The behavior of the various exercise end points in the different trial phases is shown in Table 2 and Figure 1.

Relative to placebo, immediate patch application improved exercise capacity: time to 1 mm ST segment depression increased from 471 ± 226 to 590 ± 213 s ($p < 0.05$) and total exercise time also increased from 562 ± 227 to 631 ± 219 s (p = NS). Heart rate, systolic blood pressure and

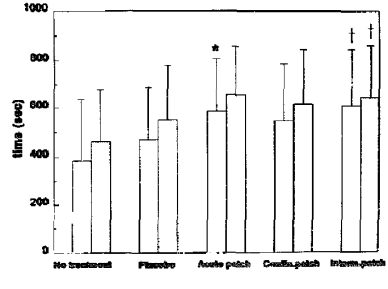


Figure 1. Results of exercise stress testing. Time to 1 mm of ST segment depression (white bars) and total exercise time (shaded bars) were recorded in each trial phase. Relative to placebo, time to 1 mm of ST depression was significantly longer during immediate patch application (*$p < 0.05$) and intermittent treatment (Interm. patch) (†$p < 0.01$). Contin. patch = continuous patch application.

Table 3. Ischemic Episodes Recorded During Holter Monitoring

	No Patch		Placebo		Acute		Continuous		Intermittent	
Pt No.	8 AM to Midnight	Midnight to 8 AM	8 AM to Midnight	Midnight to 8 AM	8 AM to Midnight	Midnight to 8 AM	8 AM to Midnight	Midnight to 8 AM	8 AM to Midnight	Midnight to 8 AM
1	3	—	1	—	2	1	4	—	3	1
2	1	—	1	—	1	—	3	—	3	—
3	2	—	3	—	5	—	2	—	1	—
4	3	—	2	—	4	—	6	—	1	—
5	3	6	1	2	1	4	2	1	2	2
6	3	—	3	—	1	—	1	—	4	1
7	1	2	6	—	1	1	1	1	2	—
8	1	—	4	1	1	—	1	—	2	1
9	1	—	1	—	1	—	1	—	1	—
10	1	1	3	—	3	2	2	—	2	1
11	3	2	3	1	2	1	2	3	1	1
12	2	1	2	—	1	—	4	2	1	—

Numbers indicate episodes observed from 8 AM to midnight and from midnight to 8 AM. Pt = patient.

rate-pressure product at the onset of ischemia (1 mm ST segment depression) and at peak exercise were not significantly different from values with placebo.

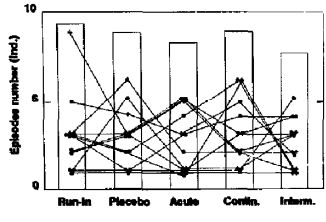
On maintenance intermittent treatment, time to 1 mm of ST segment depression and total exercise time (601 ± 236 and 651 ± 213 s, respectively) were significantly greater than with placebo administration ($p < 0.01$) but were not significantly different from values during continuous dosing (540 ± 251 and 610 ± 231 s, respectively, $p = NS$). During intermittent dosing, heart rate and systolic blood pressure at 1 mm of ST segment depression (125 ± 14 beats/min and 170 ± 11 mm Hg) were higher than with placebo administration (117 ± 11 beats/min and 160 ± 20 mm Hg, respectively, $p < 0.05$), but no significant changes in these variables were noted between continuous and intermittent therapy.

Holter monitoring. The results obtained by ambulatory ECG monitoring during the different treatment phases in individual patients are shown in Table 3. In the 60 24-h recordings obtained in the 12 patients, we observed a total of 168 episodes of ischemic ST segment depression, of which 54 (32%) were associated with angina; 128 (76%) occurred between 8 AM and midnight and 40 (24%) from midnight to 8 AM. In the individual patients, the number of ischemic episodes during the 24 h ranged from one to nine.

No statistically significant differences were found in the number, severity and duration of ischemic attacks recorded during the different trial phases. Of the 168 episodes, 36 occurred during the no patch period, 34 during placebo administration, 32 during immediate patch application and 35 during continuous and 30 during intermittent treatment (Fig. 2). Similarly, total ischemic time was 628 min during the no patch period, 483 min during placebo administration, 443 min during active nitroglycerin patch application and 439 min during continuous and 593 min during intermittent treatment (Fig. 3). Similarly, transdermal nitroglycerin patches did not affect the diurnal distribution of ischemic attacks; in fact, during continuous treatment, the mean number of episodes recorded during the daytime (from 8 AM to midnight) and during the night (from midnight to 8 AM) was 2.4 ± 1.6 and 0.6 ± 1.0, respectively; during intermittent therapy, an average of 1.9 ± 1.0 and 0.6 ± 0.7 episodes, respectively, was recorded. These values were not significantly different from those obtained with placebo (2.5 ± 1.5 and 0.3 ± 0.7, respectively). Finally, the ECG severity of ischemic episodes apparently was not affected by transdermal nitroglycerin and the percent of episodes with 1, 2 and 3 mm of ST segment depression remained practically unchanged during the various trial phases.

Subjective assessment. Of the 14 patients initially enrolled, 2 discontinued treatment because of severe headache; in the remaining 12, the nitroglycerin patches were well tolerated. No other side effects were noted. The overall incidence of anginal attacks during the investigation was low and there was no evidence of exacerbation of angina during overnight patch removal in the intermittent phase compared with the continuous phase.

Figure 2. Ischemic episodes recorded during ambulatory monitoring. Columns indicate the total number of events observed during each trial phase. For each of the 12 patients (lines), the number of ischemic episodes is indicated by points. Contin. = continuous patch application; Ind. = individual patients; Interm. = intermittent patch application; Run-in = no patch.



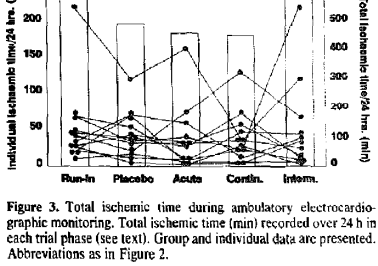


Figure 3. Total ischemic time during ambulatory electrocardiographic monitoring. Total ischemic time (min) recorded over 24 h in each trial phase (see text). Group and individual data are presented. Abbreviations as in Figure 2.

Despite the lack of objective evidence of anti-ischemic effects, daily anginal episodes were significantly less ($p < 0.05$) during both continuous (1.3 ± 0.8) and intermittent (1.2 ± 0.6) treatment than during placebo (2.2 ± 1.6).

Discussion

Present findings. Our findings confirm and extend the results of previous reports and indicate that although nitroglycerin patches afford some improvement in exercise capacity in the very early phase of treatment, tolerance rapidly develops when these preparations are used continuously. In fact, no significant prolongation in exercise duration and time to ischemia was found when transdermal nitroglycerin was given continuously for 12 days, whereas a slight but statistically significant improvement was observed when the patch was removed overnight.

However, the improvement in exercise tolerance observed with the intermittent dosing schedule was not maintained during daily activities. In fact, analysis of ambulatory ECG recordings showed no significant differences among the various treatment phases. Neither continuous nor intermittent administration of transdermal nitroglycerin appeared to affect the number, severity, duration and diurnal distribution of ischemic events.

Relation to previous studies. Our data support the results obtained by Fox et al. (22), who also studied the effects of continuous and intermittent transdermal nitroglycerin and used both exercise testing and ambulatory ST segment monitoring as objective end points. However, in that study, angiographic evidence of the presence and severity of coronary artery disease was not provided and the trial was conducted on two separate study groups—one treated continuously and the other intermittently.

The discrepancy between the results of exercise stress testing and those obtained by Holter monitoring has also been reported by others (21,22) and is difficult to explain. It could be argued that our study patients were monitored for only 24 h and that this could have partially accounted for our negative results. However, Fox et al. (22), who employed a 48-h monitoring period, also failed to show a significant anti-ischemic effect of transdermal nitroglycerin. It is possible that the lack of efficacy on daily life ischemia relates to inconstant drug plasma levels and to the fact that episodes occurring during normal activities are probably caused by a variety of pathophysiologic mechanisms, not all necessarily prevented by transdermal nitrates.

Surprisingly, despite the lack of objective evidence for anti-ischemic effects, the frequency of anginal attacks reported during intermittent and continuous treatment was significantly lower than with placebo. The observation is in keeping with the results of open studies (28) in which the efficacy of transdermal nitrates was evaluated by the effects on symptoms and could be related to the reduction in cardiac volume and left ventricular filling pressure induced by nitrates. In fact, although the mechanisms of cardiac ischemic pain are largely unknown, experimental studies suggest that nonspecific "polymodal" receptors (29) and, particularly, ventricular stretch receptors activated by changes in preload (30) are probably involved in mediating angina.

A crucial point regarding the use of intermittent nitrate preparations relates to the possibility that drug withdrawal during treatment-free intervals may exacerbate ischemic events, especially if asymptomatic. The results of our study do not support this hypothesis and show that despite a lower nitroglycerin dose delivered over the 24 h (6.6 rather than 10 mg), the intermittent schedule was not associated with worsening of ischemia.

Conclusions. Our study confirms and extends previous reports (15–18) by showing that intermittent transcutaneous nitroglycerin dosing does not cause tolerance and improves exercise capacity in patients with stable angina. Furthermore, it provides the first objective demonstration that this formulation, despite reducing the frequency of anginal attacks, does not affect the number and severity of silent ischemic events that occur during normal daily activities regardless of the type of dosing schedule. This finding suggests that the anti-ischemic effects of transdermal nitroglycerin are probably too mild when the drug is not supplemented by other antianginal medications. Finally, in patients with chronic stable angina, intermittent dosing schedules do not appear to cause exacerbation of ischemic events during overnight withdrawal. Whether this also applies to more severe forms of angina remains to be established.

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